Amendments to the Claims

Please cancel Claims 1-22, 24, 29-32, 34-58, 61 and 63-65. Please amend Claims 23, 26-28, 59, 60 and 62. The Claim Listing below will replace all prior versions of the claims in the application:

Claim Listing

1. through 22. (Canceled)

23. (Currently amended) A method for identifying genes that carry one or more harmful allele, comprising:

a) identifying in one or more samples one or more inherited point mutations that are found in one or more genes or portions thereof of a population of young individuals, determining the frequency with which each point mutation occurs, and calculating the sum of the frequencies of all point mutations identified for each gene or segment;

b) identifying in one or more samples one or more inherited point mutations that are found in one or more genes or portions thereof of a population of aged individuals, determining the frequency with which each point mutation occurs, and calculating the sum of the frequencies of all point mutations identified for each gene or segment;

c) comparing the sum of the frequencies of point mutations that are found in a selected gene or portion thereof of the young population calculated in a) with the sum of the frequencies of point mutations that are found in the same gene or portion thereof of the aged population calculated in b), wherein a significant decrease in the sum of the frequencies of point mutations in the aged population indicates that said selected gene carries one or more harmful allele.

24. (Canceled)

25. (Previously presented) A method for identifying genes that carry a harmful allele, comprising:

a) identifying the set of inherited point mutations that are found in one or more genes or portions thereof of a population of young individuals, wherein the set comprises all inherited point mutations occurring at a frequency at about or above 5×10^{-5}, and determining the frequency with which each point mutation occurs;

b) identifying the set of inherited point mutations that are found in the genes or portions thereof of a population of aged individuals, and determining the frequency with which each point mutation occurs; and

c) comparing the frequency of each point mutation identified in a selected gene or portion thereof of the young population determined in a) with the frequency of the same point mutations identified in said selected gene of the aged population determined in b), wherein a significant decrease in the frequency of two or more point mutations in said selected gene of the aged population relative to said selected gene of the young population indicates that said selected gene carries a harmful allele.

26. (Currently amended)The method of Claim 25 further comprising:

d) determining the frequency of ~~said~~ two or more point mutations that decrease in the aged population determined in c) in ~~said selected gene of~~ one or more intermediate age-specific populations;

e) determining the age-specific decrease in frequency of said two or more point mutations; and

f) comparing the age-specific decrease in frequency ~~determined in e)~~ with the expected age-specific decrease in frequency of a set of harmful alleles that cause a particular mortal diseases, ~~and determining if the functions are significantly different,~~

wherein a determination that the age-specific decrease in frequency determined in e) is not significantly different from the expected age-specific decrease in frequency of

harmful alleles further indicates that said selected gene carries a harmful allele and has a high probability of being causal of said ~~one or more~~ mortal disease ~~diseases~~.

27. (Currently amended) The method of Claim 26 further comprising:

g) determining the frequency of said two or more point mutations that ~~which~~ decrease in the aged population in said selected gene of one or more proband populations; and

h) comparing the frequencies of said two or more point mutations in said selected gene or portion thereof in the young population with the frequencies of said two or more point mutations in said selected gene or portion thereof in the proband populations,

wherein a significant increase in the frequencies of said one or more point mutations in the proband population relative to the young population indicates that said gene caries a harmful allele that plays a causal role in said disease.

28. (Currently amended) The method of Claim 26 further comprising:

g) determining the frequency of said two or more point mutations that ~~which~~ decrease in the aged population in said selected gene of one or more proband populations consisting of individuals with early onset disease; and

h) comparing the frequencies of said two or more point mutations in said selected gene or portion thereof in the young population with the frequencies of said two or more point mutations in said selected gene or portion thereof in the proband populations,

wherein a significant increase in the frequencies of said one or more point mutations in the proband population relative to the young population indicates that said gene carries a harmful allele that ~~which~~ is a secondary risk factor ~~which accelerates the appearance of disease~~.

29. throguh 32. (Canceled)

33. (Previously presented) A method for identifying genes that carry a harmful allele or that are linked to a gene that carries a harmful allele, comprising:

a) identifying the set of inherited point mutations that are found in one or more genes or portions thereof of a population of young individuals, wherein the set comprises all inherited point mutations occurring at a frequency at about or above 5×10^{-5}, and determining the frequency with which each point mutation occurs;

b) identifying the set of inherited point mutations that are found in the genes or portions thereof of a population of aged individuals, and determining the frequency with which each point mutation occurs;

c) comparing the frequency of each point mutation identified in a selected gene or portion thereof of the young population determined in a) with the frequency of the same point mutations identified in said selected gene of the aged population determined in b), wherein a significant decrease in the frequency of a point mutation in said selected gene of the aged population relative to said selected gene of the young population indicates that said selected gene carries a harmful allele or is linked to a gene that carries a harmful allele.

34. though 58. (Canceled)

59. (Currently amended) A method of identifying one or more inherited point mutations in any target region of a genome of a population, wherein said point mutations cause or accelerate the appearance of a mortal disease or prevent or delay the appearance of a mortal disease, comprising:

a) <u>separately</u> determining the set of all inherited point mutations occurring at a frequency at or above 5×10^{-5} ~~separately~~ in members of the same population that comprises subpopulations selected from the group consisting of young, aged, intermediate age, afflicted with disease, afflicted with a disease of early age onset and afflicted with a disease of late age onset; and

b) determining the frequencies of each inherited point mutation within ~~and between~~ the subpopulations,

wherein a decrease in the frequency in the aged population compared to the young population is indicative of an allele that causes or accelerates a mortal disease, and an increase in frequency in the intermediate or aged population compared to the young population is indicative of an allele that prevents or delays the appearance of a mortal disease.

60. (Currently amended) The method of Claim 25, wherein said inherited point mutations are identified using a method that comprises:

a) providing a first pool of DNA fragments comprising a gene or portion thereof, wherein said pool is isolated from a population;

b) amplifying a target region of said gene or portion from each of said fragments in a high fidelity polymerase chain reaction (PCR) under conditions suitable to produce double-stranded ~~double stranded~~ DNA products that ~~which~~ contain a terminal high temperature isomelting domain that is labeled with a detectable label, and wherein ~~where~~ the mutant fraction of each PCR-induced mutation is not greater than about 5×10^{-5};

c) melting and reannealing the product of b) under conditions suitable to form duplexed DNA, thereby producing a mixture of wild-type ~~wild type~~ homoduplexes and heteroduplexes that ~~which~~ contain point mutations;

d) separating the heteroduplexes from the homoduplexes based upon the differential melting temperatures of said heteroduplexes and said homoduplexes and recovering the heteroduplexes, thereby producing a second pool of DNA that is enriched in target regions containing point mutations;

e) amplifying said second pool by ~~in a~~ high fidelity PCR under conditions where only homoduplexed double-stranded ~~double stranded~~ DNA is produced, thereby producing a mixture of homoduplexed DNA containing wild-type ~~wild type~~ target region and homoduplexed DNAs that ~~which~~ contain target regions that include point mutations;

f) resolving the homoduplexed DNAs containing target regions that ~~which~~ include point mutations based upon the differential melting temperatures of the DNAs,

and recovering the resolved DNAs that ~~which~~ contain a target region that ~~which~~ includes point mutations; and

g) determining the sequence of the target region of the recovered DNAs to identify point mutations within the target region.

61. (Canceled)

62. (Currently amended) A method for identifying genes that carry one or more harmful alleles, comprising:

a) identifying in one or more samples one or more inherited point mutations that are found in one or more genes or portions thereof of a population of young individuals, determining the frequency with which each point mutation occurs, and calculating the sum of the frequencies of all point mutations identified for each gene or segment;

b) identifying in one or more samples one or more inherited point mutations that are found in one or more genes or portions thereof of a population of aged individuals, determining the frequency with which each point mutation occurs, and calculating the sum of the frequencies of all point mutations identified for each gene or segment;

c) determining the point mutations that are obligatory knock-out ~~knockout~~ point mutations; and

d) comparing the sum of the frequencies of obligatory knock-out ~~knockout~~ mutations that are found in a selected gene or portion thereof of the young population calculated in a) with the sum of the frequencies of point mutations that are found in the same gene or portion thereof of the aged population calculated in b),

wherein a significant decrease in the sum of the frequencies of point mutations in the aged population indicates that said selected gene carries one or more harmful alleles.

63. through 65. (Canceled)